NON-TECHNICAL ABSTRACT: SCH 412499 (RAD- $P21^{WAF1/CIP}$)

Glaucoma is the leading cause of irreversible blindness both in the United States and worldwide. The disease is characterized by elevation of the pressure in the eye (intraocular pressure; "IOP") resulting in degeneration of the optic nerve and loss of vision. The majority of therapies to treat glaucoma are directed at lowering IOP. Glaucoma filtration surgery (trabeculectomy) reduces IOP through a procedure that creates a small drainage hole in the eye. Glaucoma surgery failure results from normal wound healing response that blocks the surgically created hole. This healing causes IOP to rise again, indicating the surgery has failed. Part of this wound healing response is due to the growth of cells at the surgical site. The failure rate is as high as 50% at 2 years, and higher in certain patients. Drugs that block cell growth have improved the long-term success rate of this surgery. However, these drugs have been associated with serious side effects, some of which can be blinding. As such, there is a need to develop an improved way to prevent surgical failure without these side effects.

This Phase I study will determine the safety of a gene therapy drug that is designed to block the cell growth mentioned above. A gene, called $p21^{WAF1/Cip1}$ and whose normal function in a cell is to inhibit growth, will be delivered to the eye. The gene, carried by a modified cold virus ("adenovirus") will be delivered by injection under the conjunctiva ('skin' of the eye) one day prior to surgery.

Laboratory experiments have shown that this gene/virus combination (called "SCH 412499") inhibits the growth of cells in the eye. Surgical studies in rabbits have shown that SCH 412499 prolonged surgical success when delivered one day before surgery. Treatment with SCH 412499 in the eyes of monkeys with high IOP resulted in IOP lowering following trabeculectomy. Importantly, the side effects seen with the other drugs mentioned above have not been seen with SCH 412499 in either rabbits or monkeys. Decreasing IOP is the goal for future clinical trials with SCH 412499. Non-clinical safety testing in monkeys has been completed and the

results support the initiation of human trials. The proposed clinical study is intended to look at the safety of SCH 412499 in humans.